REMARKS

Claims 1-12, 14-32, and 43-44 have been withdrawn. Claims 13, 33, 35, 37, and 39-41 have been cancelled. Claims 34, 36, 38, 42, and new claims 45-46 are pending in this application. Claim 34 has been written in independent format and includes a limitation of claim 37. Claim 42 has been amended in view of the disclosure in the specification (US 2004/0192690: page 3, at 0043 and 0057; page 4 at 0074).

Claim 13 has been rejected under 35 USC §102(b) by the Examiner as being anticipated by Jao *et al.* (U.S. 5,955,103). In as much as this claim has been cancelled, this rejection is now moot.

The Examiner has rejected Claim 13 under 35 USC §102(e) as being anticipated by Nadkarni (WO 03/104192). Since this claim has been cancelled, this rejection is, likewise, now moot.

Claims 33-42 have been rejected under 35 USC §103 by the Examiner as being unpatentable over Nadkarni (WO 03/104192) in view of Staniforth (U.S. 5,004,914).

It is the Examiner's position that it would have been obvious to one of ordinary skill in the art at the time of the invention to make a sustained release formulation of lamotrigine with an outer coat covering said core impermeable to environment fluids because of the teachings of Nadkarni and Staniforth. According to the Examiner, Nadkarni teaches that the advantage of controlled release of a drug is to provide therapeutically effective level of an agent for an extended period of time and longer period of pharmacological and diagnostic response and teaches sustained release formulation of lamotrigine. Staniforth, according to the Examiner, teaches a different technique of controlled release formulation of drugs by adjusting the thickness of the outer coating so that it is substantially impermeable to the entrance of an environmental fluid present in an environment of use and substantially impermeable to the exit of said active agent during a dispensing period. Hence, the Examiner concludes, one of ordinary skill in the art would have been motivated to combine the teachings of Nadkarni with Staniforth to provide a sustained release formulation of lamotrigine with an outer coating that is impermeable to environmental fluid and impermeable to the exit of an active agent such as lamotrigine.

Applicants' problem to be solved is to provide a sustained release formulation of lamotrigine that releases drug between the stomach and ascending colon (US 2004/0192690, page 1 at 0021-0022). That is, Applicants' formulation releases drug at two different sites – the stomach (acidic environment) and the small intestines (basic environment).

The present invention as claimed has a core with an outer coat which includes one or more orifices and dissolves when the surrounding pH exceeds 5. Until the outer coat dissolves in a high pH environment (the intestine), lamotrigine is only released from the core via the holes in the outer coat. This slows the release of lamotrigine in the stomach compared with the intestine where the whole core is exposed by the outer coat's disintegration in the high pH environment. Lamotrigine is absorbed evenly along the gastrointestinal tract, but is more soluble in the stomach compared to lower regions in the gastrointestinal tract. By limiting the rate of release of lamotrigine in the stomach compared with the intestine, the plasma profile of lamotrigine levels out and reduces the adverse events and breakthrough symptoms.

Nadkarni provides a formulation that has been designed to provide a once daily dose of lamotrigine that can be taken without water or can be dispersed in water for the convenience of patients (p. 3, lines 29-33). The formulation comprises lamotrigine particles, a release rate controlling polymer and a rapidly disintegrating binder. The rapidly disintegrating binder allows the particles to rapidly disperse in an aqueous environment (p. 4, lines 21-27). This means that once the formulation is taken orally, the dosage form breaks up. The rate of release of the lamotrigine in the particles is then dependent on the nature of the release rate controlling polymer.

Applicants' claimed invention does not use a rapidly disintegrating binder for dispersion in the mouth or in water as required by Nadkarni. Applicants' formulation is formulated with attention to the stomach and intestine environments, not to the mouth or water/suspension environments as Nadkarni is. Applicants' formulation has an outer coating and orifice(s).

Staniforth does not teach or suggest a lamotrigine formulation. Staniforth seeks to maintain the concentration of an active agent at a predetermined site for an extended period of time ('614, column 1, lines 15-18). This reference discloses a device for controlled release of an active agent comprising (i) a core comprising the

active agent and a release modifying agent and (ii) an outer coating that is substantially impermeable to the entrance of an environmental fluid and substantially impermeable to the exit of active agent during a dispensing period, said outer coating including (iii) an orifice extending through said coating but not penetrating said core and communicating from said environment of use to said core for allowing the release of said active agent into said environment of use. The Examiner acknowledges that Staniforth does not teach a coating that dissolves at pH above 5, nor does this reference disclose a value for the thickness of the outer coating/polymer as in Applicants' claim 38 or 39.

In the stomach, the Staniforth tablet releases active ingredient through the orifices in the coating, and some of the stomach contents (including the active ingredient) trickle through to the small intestine where the active ingredient is absorbed. When the tablet itself moves out of the stomach and into the small intestine, active ingredient continues to be released through the orifice(s) in the coating and absorbed. However, the tablet may move into the lower (large) intestine before the remainder of the active ingredient in the tablet can be released through the orifice(s) in the coating.

In contrast, in the small intestines, a tablet employing Applicants' claimed formulation with core, orifices, a coating that dissolves above pH 5 results in the coating disintegrating such that all of the drug/lamotrigine is released for patient utilization.

Neither Staniforth nor Nadkarni teach an outer coating that dissolves at pH above 5. Applicants' Claim 34 as amended describes a sustained release formulation of lamotrigine in a core coated in a substantially impermeable outer coating with openings, said coating dissolving at pH above 5. This formulation would not have been obvious to a skilled person and could not be predicted from the combined teaching of Nadkarni and Staniforth. It is only from first having read Applicants' disclosure that one skilled in the art would omit Nadkarni's rapidly disintegrating binder thereby destroying the Nadkarni invention, choose Staniforth's impermeable coating with orifice(s). And neither reference teaches or appreciates the need for a coating dissolving at pH above 5 which limitation is found only in Applicants' claims. The combination of a impermeable coat with orifice(s) and its coating dissolution at pH above 5 means that there is a steady release of

lamotrogine through the orifice(s) in the coating while the tablet is in the stomach (pH below 5) and in the small intestine the coating then dissolves, releasing the remainder of the lamotrogine contained in the core. This is nowhere taught or suggested by either of the cited references alone or by their combination. Accordingly, this rejection of the claims should be reconsidered and withdrawn.

The Examiner has not acknowledged receipt of the certified copies of the priority documents. Applicants note that the copies were filed on July 29, 2003 in parent Application No. 10/629,177, now abandoned. It is believed that additional certified copies are not required in the present application. Applicants respectfully request that the Examiner acknowledge receipt in the next Office communication.

Accordingly, it is respectfully requested that all rejections of the claims be reconsidered and withdrawn and that the application as amended be allowed.

The Commissioner is hereby authorized to charge any fees required or credit any overpayment to Deposit Account No. 07-1392.

Respectfully submitted,

Date: 17 September 2007

Bonnie L. Deppenbrock
Attorney for Applicants
Registration No. 28,209

Customer No. 23347
GlaxoSmithKline
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709
Telephone: (919) 483-1577
Facsimile: (919) 483-7988

ELECTRONICALLY FILED USING THE EFS-WEB ELECTRONIC FILING SYSTEM OF THE UNITED STATES PATENT & TRADEMARK OFFICE ON 9/17/07.